FINAL ACTION

1. Applicant's amendment and response filed June 20, 2008 are acknowledged. Claims 1-93, 104 and 108-130 are canceled. Claims 94-95, 100, 103, 105-107, 132-134, 136 and 137-146 are amended. Claims 94-95, 99-103, 105-107 and 131-146 are under examination.

2. For clarification of the record, a typographical error was made on page 12, paragraph 8 of the last office action mailed December 7, 2007. The enablement rejection under 35 U.S.C. 112 first paragraph is made over claims 94-95, 99-103, 105-107 and 131-146 *and not* -95, 99-103, 106-107 and 131-146. The Office apologizes for the mistake.

Rejections Withdrawn

3. In view of Applicant's amendment and response the following rejections have been withdrawn:

a) objection to claim 94, page 4, paragraph 5.

b) rejection of claims 139-146 under 35 U.S.C. 112 first paragraph, Biological Deposit, pages 4-8, paragraph 6.

c) rejection of claims 106, 134 and 142 under 35 U.S.C. 112 second paragraph, page 17, paragraph 9.

d) rejection of claims 107 and 131-133 under 35 U.S.C. 112 second paragraph, page 17, paragraph 10.

e) rejection of claims 107, 131-133 and 141-144 under 35 U.S.C. 112 second paragraph, pages 17-18, paragraph 11.

f) rejection of claims 136 and 144 under 35 U.S.C. 112 second paragraph, pages 18, paragraph 12.

g) rejection of claims 107 and 131-138 under 35 U.S.C. 112 second paragraph, pages 18, paragraph 14.

h) rejection of claims 138 under 35 U.S.C. 112 second paragraph, pages 18, paragraph 14.

Rejections Maintained

4. The rejection under 35 U.S.C. 112 first paragraph is maintained for claims 134 and 142 for the reasons set forth on pages 8-12 paragraph 7 of the previous Office Action.

The rejection is reiterated below:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement Regarding Fragments

Claims 134 and 142 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *Chlamydia trachomatis* high molecular weight protein (HMW) or the *Chlamydia* major outer membrane protein (MOMP), does not reasonably provide enablement for fragments of the *Chlamydia trachomatis* high molecular weight protein (HMW) or the *Chlamydia* major outer membrane protein (MOMP). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches that compositions comprising PMPE proteins of the invention and the other immunogens such as the *Chlamydia trachomatis* high molecular weight protein (HMW) or the *Chlamydia* major outer membrane protein (MOMP) (page 43). The claims are directed to sequences that are fragments of the *Chlamydia trachomatis* high molecular weight protein (HMW) or the *Chlamydia* major outer membrane protein (MOMP), There is no guidance provided as to which amino acids can be deleted and still have the polypeptide retain its biological function. Thus, the resulting polypeptide could result in a polypeptide not taught nor enabled by the specification.

Thomas E. Creighton, in his book, "*Proteins: Structures and Molecular Properties, 1984",* (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a proline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "*Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "*Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in an amino acid's sequence and still retain similar activity requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide's structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would not expect any tolerance to multiple deletions. There is no guidance provided in the specification as how one would begin to choose "fragments" of the *Chlamydia trachomatis* high molecular weight protein (HMW) or the *Chlamydia* major outer membrane protein (MOMP),. The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which the retain the biological activity if the intact polypeptide; and
- the specification provides essentially no guidance as to which of the essentially infinite possible choice is likely to be successful.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other polypeptides having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptide that are fragments of the *Chlamydia trachomatis* high molecular weight protein (HMW) or the *Chlamydia* major outer membrane protein (MOMP), in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of deletions or fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the polypeptide's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd.

927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

Applicant's Arguments

Applicant urges that to enabled, a claimed invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. Applicant urges that the specification need not explicitly teach those in the art to make and use the invention, the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without undue experimentation. Applicant urges that both claims 134 and 142 depend from claims 132 and 139, respectively, which are each directed to a vaccine composition comprising an isolated PMPE polypeptide and further comprising one or more heterologous polypeptides. Applicant urges that claims 134 and 142 further require the claimed vaccine to comprise the HMW or MOMP polypeptide of fragment thereof. Applicant urges that due to the open-ended claim language "comprises" the claimed invention can include additional elements.

Applicant urges that the HMW and MOMP polypeptides were known before the filing dated of this application. Applicant urges that the HMW and MOMP polypeptides were disclosed in WO/99/171741 filed October 1, 1998 and published April 1, 1999. Applicant urges that the polypeptides were also known in U.S. Patent No. 5,869, 608 filed March 16, 1992 and issued February 9, 1999. Applicant urges that the rejection should be withdrawn.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed June 20, 2008 have been fully considered but they are not persuasive.

It is the Examiner's position that the claimed invention which includes fragments and the instant specification has not shown enablement for fragments of HMW or MOMP polypeptides. The specification fails to provide guidance as to which amino acids can be deleted and the polypeptides still retain their claimed biological function of providing protective immunity (e.g. a vaccine). It should be noted that the 35 U.S.C. 112 first paragraph requires that Applicant teach how to "make and use" the claimed invention not how to "find" fragments of HMW or MOMP that are capable of providing protective immunity. A structural description is required and the structural description must correlate with the intended function of the polypeptides. Undue experimentation would be required to select fragments of HMW or MOMP polypeptides.

While use of BLAST and other sequence comparison tools are known, it is not routine in the art to screen for multiple deletions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. The claims broadly encompass a broad genus of polypeptides. One skilled in the art would require guidance in order to make and use HMW or MOMP polypeptides. Without such guidance the experimentation to arrive at the claimed invention would be undue. One skilled in the

art would conclude that the instant specification has enabled the broadly claimed genus of polypeptides by the information disclosed in the specification.

To address Applicant's comments regarding HMW and MOMP polypeptides being known in the art, while HMW and MOMP polypeptide may be known in the art the instant specification nor the art has demonstrated that the HMW or MOMP polypeptides or fragments thereof can function as a vaccine and provide protective immunity.

To address Applicant's comments regarding the open-ended claim language comprising, while the vaccine compositions comprising HMW or MOMP polypeptides or fragments thereof may comprise other elements, the claimed composition must provide the function of protective immunity since it is a vaccine. There is no guidance as to how one of skill in the art would select HMW or MOMP polypeptide fragments that are capable of providing protective immunity against *Chlamydia trachomatis* infections.

In view of all of the above this rejection is maintained.

5. The rejection under 35 U.S.C. 112 first paragraph is maintained for claims 94-95, 99-103, 105-107 and 131-146 for the reasons set forth on pages 12-16, paragraph 8 of the previous Office Action.

The rejection is reiterated below.

Scope of Enablement Regarding Vaccine Compositions

Claims 94, 95, 99-103, 105-107 and 131-146 rejected under 35 U.S.C. 112, first paragraph, because the specification, while enable for immunogenic compositions that produce an immune response in a subject does not provide enablement for a *vaccine compositions* wherein the effective amount of said vaccine composition administered to subjects provide *protective immunity.* In the case of independent claim 107, the specification does not provide enablement for recited limitation "wherein an effective amount of said vaccine administered to female mice reduces *Chlamydia trachomatis*-

induced infertility. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Independent claim 94 is directed to a vaccine comprising an isolated recombinant PMPE polypeptide comprising a polypeptide encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO;1 fused to a nucleic acid molecule encoding a histidine affinity ($(H)_6$) domain.

Independent claim 95 is directed to a vaccine comprising an isolated recombinant PMPE polypeptide comprising the amino acid sequence of SEQ ID NO:2 fused to an amino acid sequence comprising a histidine affinity ($(H)_6$) domain.

Independent claim 107 is directed to a vaccine comprising an isolated polypeptide comprising the mature putative membrane protein E (pmpE) encoded by SEQ ID No.2 and a carrier wherein an effective amount of said vaccine administered to female mice reduces *Chlamydia trachomatis*-induced infertility.

Independent claim 139 is directed to vaccine comprising an isolated polypeptide comprising the mature putative membrane protein E (pmpE) inserted in plasmid M15pREP (pQE-pmpE Ct) #37 deposited under ATCC Accession No. PTA-2462 and a carrier wherein an effective amount of said vaccine administered to female mice reduces *Chlamydia trachomatis*-induced infertility.

The specification fails to enable the claimed vaccine compositions encompassed by the claims. The term *"vaccine"* encompasses the ability of the specific antigen to *induce protective immunity* to *Chlamydia* infection or disease induction. The specification at section 6.9 discloses in an *in vitro* neutralization model and a mouse model of salpingitis and fertility. The Examples do not disclose any data as a result of the disclosed experiments. The only data disclosed in regards to these experiments is represented in Figure 7. Figure 7 merely shows that T-cell proliferation (e.g. immune responses were induced). There is no data disclosed in the instant specification leading one of skilled in the art to conclude that the instant specification shows that the claimed vaccine compositions are protective.

The specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of protecting against *Chlamydia* infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccine compositions , i.e. would not be able to accurately predict if protective immunity has been induced. The specification further does not disclose any examples demonstrating *in vivo* use of the claimed polypeptides. An *in vivo* example, would aid in answering question such as what mode of administration of the claimed polypeptides can be used to ensure that the claimed polypeptides reach the target organs in order to protect against *Chlamydia* infections?

The ability to reasonably predict the capacity of a single bacterial immunogen or combinations of immunogens to induce protective immunity against *Chlamydia* infection is problematic. Longbottom et al *(Journal of Medical Microbiology 52, p. 537-540)* teach in terms of *Chlamydia* animal infections there are problems associated with

asymptomatic infections (page 537). Longbottom et al teach that the relative contribution of antibody to resolve *Chlamydia* infections is still a matter of debate (page 538). Longbottom et al teach that studies in guinea pig models for human genital tract infections have demonstrated a role for antibody in *limiting* primary infections (page 538). Longbottom et al teach that *there is no requirement for antibody* in murine models (page 538).

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Based on the teaching of the cited art, it is unclear as to whether antibodies have a role in protecting against *Chlamydia* infections. The instant specification has shown that there are cellular and humoral immune responses elicited when animals are administered the polypeptides of the invention. However, the specification has failed to show that these polypeptides provide protection against *Chlamydia* disease or infection when administered to animals. Thus, the specification does not provide enablement for the claimed vaccine compositions encompassed by the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to developing a *Chlamydia* vaccine that would achieve a desire level of success when administered to a patient with *Chlamydia* infections, 3) there are no working examples which suggest the desired results of a successful vaccine composition that can protect against *Chlamydia* infection, 4) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention.

Applicant's Arguments

Applicant urges that the instant specification need not explicitly teach those in the art to make and use the invention where the knowledge is in the art.

Applicant urges that in support of the claims, Applicant submitted a Supplemental Declaration under 37 C.R.F. 1.132 on November 16, 2007. Applicant urges that in support of the claims they submitted a Supplemental Declaration under 35 C.F.R. 1.132 on November 16, 2007. Applicant urges that the Supplemental Declaration provided that "post filing data demonstrated that immunization with a vaccine comprising the serovar L2 PMPE polypeptide purified as described in Examples 6.13 and 6.15 of the present application reduced infertility induced by *C. trachomatis* serovar F in a standard vaginal infectivity and fertility animal models of *C. trachomatis* disease."

Applicant refers to paragraph 18 of the Supplemental Declaration under 37 C.R.F. 1.132 on November 16, 2007 which cites application 10/398, 248 which claims priority to International Application No. PCT/US01/30345 and is a continuation-in-part of this application to support their position.

Applicant urges that they submitted post-filing data showing the result of Example 6.9.2 as exhibit B on December 3, 2001 along with the amendment and reply under 37 C.F.R. 1.111. Applicant urges that Exhibit B is a table that is identical to the Table 4 disclosed in application no. 10/398, 248. Applicant urges that they have submitted sufficient post-filing data demonstrating the protective immunity of the PMPE vaccine composition.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed June 20, 2008 have been fully considered but they are not persuasive.

The Supplemental Declaration under 37 CFR 1.132 submitted by W. James Jackson filed November 16, 2007 is insufficient to overcome the rejection of claims 94-95, 99-103, 105-107 and 131-146 based upon disclosure as set forth in the last Office action because the Declaration does not show enablement for a vaccine composition comprising an isolated recombinant PMPE polypeptide.

The Declaration appears to be an opinion declaration.

In the declaration, Dr. Jackson discusses the following:

a) the work of Probst which describes identifying DNA sequences and predicted amino acid sequences of various Chlamydia antigens including the surface protein pmpA, pmpB, pmpC, pmpD, pmpE, pmpF, pmpG, pmpH and pmpI.

b) the work of Murdin which discloses a recombinant poliovirus which expresses a well-characterized neutralization epitope from the major outer membrane protein (MOMP) of C. trachomatis serovar A .

c) Exhibits B, which discloses fertility assessment data for the pmpE polypeptide, and C-H, which are journal articles that assess the state of art the regarding *Chlamydia* polypeptides and vaccines.

None of these journal articles nor the fertility assessment data teach a vaccine composition comprising an isolated recombinant PMPE polypeptide which provide protective immunity against *Chlamydia trachomatis* infections.

To address Applicant's comments regarding examples 6.13 and 6.15 of the present application, it should be noted that these examples merely show expression of recombinant PMPE and affinity chromatography purification of the PMPE polypeptide, respectively. Nowhere in these examples is protective immunity shown. It should be noted that the term "vaccine" encompasses the ability of an antigen to induce protective immunity. The post-filing data as a result of Example 6.9.2 as presented in Exhibit B submitted December 3, 2001 merely shows reduced fertility assessment for pmpE. The reduced fertility assessment is a method of treating *Chlamydia trachomatis* infections and not a method of preventing or protecting against *Chlamydia trachomatis* infections. A treatment of *Chlamydia trachomatis* infections is *not* the same as providing protective immunity against *Chlamydia trachomatis* infections. Applicant is claiming a vaccine composition. As stated above, a vaccine composition provides protection against an antigen. There is no demonstration presented in the instant specification, the submitted declaration and exhibits that show that the recombinant PMPE is capable of providing protective immunity against *Chlamydia trachomatis* infections.

To address Applicant's comments regarding application 10/398, 248, it should be noted this application is a continuation-in-part of this application. It should be remembered that the examination of one patent application does not have any barring on the examination on another patent application. The issues in each application are different and are directly related to the claimed invention in each application.

Applicants have not shown enablement for the claimed vaccine composition. Therefore, Applicants have not met their burden under 35 U.S.C. 112 first paragraph. 6

In view of all of the above, this rejection is maintained.

Status of Claims

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Patent Examiner, Art Unit 1645
September 11, 2008

/N. M. Minnifield/

Primary Examiner, Art Unit 1645